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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	39740-0005A	5745

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,56,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,40-47,51,52,56,57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/14/2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/04 5/05 2/06 4/0*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I in the reply filed on May 23, 2006 is acknowledged. The traversal is on the ground(s) that a search of all the claims would not present an undue burden. The arguments are not found persuasive because the inventions have acquired different status in the art as demonstrated by their different classification and recognized divergent subject matter. Further, the inventions require different searches that are not co-extensive with each other. For instance, a literature search for the method of predicting the likelihood that a colon cancer patient will respond to treatment is not co-extensive with a literature search for the method of treating a patient diagnosed with and EGFR expressing colon cancer. Further, a finding that, for example, the method of invention I is anticipated or obvious over the prior art would not necessarily extend to a finding that the method of invention II is also anticipated or obvious over the prior art. Similarly, a finding that the method of Invention I is novel and unobvious over the prior art would not necessarily extend to a finding that the method of Invention II is also novel and unobvious over the prior art. Additionally the applicant traversed the requirement to elect a single gene or combination of genes with respect to claim 60 on the basis that it is a dependent claim. However, each gene consists of a different nucleotide sequence, has a different melting temperature, a different specificity of hybridization, and encodes for a protein having a different biological activity. For example, Bak is chemically, structurally and functionally distinct from KRTI7 and therefore a search for Bak would not be co-extensive with a search for

KRTI7. Accordingly, examination of these distinct inventions would pose a serious burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

It is also noted that the applicants have amended the claims so that the claims which were originally inventions III and IV now depend from invention I. As a result claims 3, 35-39, 41-47, 51-52, and 56-61 have been examined herein.

Drawings

2. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figures 1-2 are illegible. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 35-39, 41-47, 51-52, 56-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for methods for (i) determining the normalized level of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and an increase in GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor; and (ii) determining the normalized level of the corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in the gene product of LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in the gene product of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to methods for predicting the likelihood that a colon cancer patient will respond to treatment with an EGFR inhibitor by determining the

normalized level of LAMC2, GPC3, or their corresponding gene products in a sample comprising EGFR expressing cancer cells wherein an increase in LAMC2 or its gene product is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in GPC3 or its gene product is indicative that the patient will show a increased likelihood of response to treatment with and EGFR inhibitor. The term " an EGFR inhibitor" is broad in that it includes every inhibitor in the class of EGFR inhibitors. Additionally the claims encompass methods which determine the normalized level of LAMC2 and GPC3 and the corresponding gene products. The term "the corresponding gene products" is broad in that it includes every possible amino acid product which can be produced by the LAMC2 and GPC3 genes such as those that would be produced by LAMC2 and GPC3 nucleic acids having naturally and non-naturally occurring allelic, mutant, and splice variants.

Nature of the Invention

The claims are drawn broadly to methods for predicting the likelihood that a colon cancer patient will respond to treatment with an EGFR inhibitor. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification at page 25 teaches that the EGFR is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several EGFR inhibitors are promising drug candidates

for the treatment of EGFR expressing cancers. The specification further teaches the following EGFR inhibitors: (i) Iressa is a small synthetic quinazoline that competitively inhibits the ATP binding site of EGFR and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the EGFR and EGFR-dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas. The specification also teaches several methods of gene expression profiling such as RTPCR, microarray analysis, SAGE, mass array technology etc.

Additionally the specification does not teach that LAMC2 and GPC3 are overexpressed in colon cancer. However the pre filing date art of Hlubek et al teach that the γ2 chain of laminin-5 (LAMC2) is strongly overexpressed in disseminating and infiltrating tumor cells at the invasive front of colorectal carcinomas (Abstract). Filmus et al teach that GPC3 is not normally expressed in the colon however it is expressed in a significant proportion of colorectal tumors (Page21R).

Accordingly the specification is not enabled for determining the normalized level of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with a EGFR inhibitor and a an increase in GPC3 is indicative

that the patient will show a increased likelihood of response to treatment with a EGFR inhibitor because the specification does not show data wherein a specific EFGR inhibitor (i.e. such as Iressa or Cetuximab) was used. The specification also does not provide an example for determining the normalized level of a representative number of corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in the gene product of LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in the gene product of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying if every EGFR inhibitor will be less effective in patients with increased LAMC2 levels or gene product levels and the art of identifying if every EGFR inhibitor will be more effective in patients with increased GPC3 levels or gene product levels is highly unpredictable.

The specification teaches following EGFR inhibitors: (i) Iressa; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12); (iii) Cetuximab; and (iv) Tarceva™. The specification also teaches that gene expression studies on head and neck tumors were done based on the treatment of five different EGFR inhibitor drugs. However, the specification does not teach which inhibitors are associated with the changes in the level of LAMC2 or GPC3 in head and neck cancers. The specification also teaches that gene expression studies on colon caner were done based on the treatment of an EGFR inhibitor. However, the specification does not

enable practicing the invention because it does not teach which inhibitors are associated with the changes in the level of LAMC2 or GPC3 in colon cancer. Thereby, the disclosure in the specification does not teach a representative of the broadly claimed genus of any EGFR inhibitor.

The genus of EGFR inhibitor drugs is expected to be very large. For example the post filing date art of Giaccone teach six EGFR inhibitors (Iressa, Tarceva, lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR. For example Iressa and Tarceva inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. Thus it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism.

Both LAMC2 and GPC3 are expected to be capable of producing several different gene products. The claims as written encompass all of the corresponding gene products of the LAMC2 and GPC3 genes. While the wild type LAMC2 and GPC3 nucleic acid sequences were known in the prior art, this information does not allow one to envision all possible gene LAMC2 and GPC3 gene products, including allelic, and splice mutants, as well as homologous sequences. Thus it is highly unpredictable as to whether one can determine the normalized level of a representative number of the corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR

expressing cancer cells wherein an increase in any of the gene products of LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in any of the gene products of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

Further, it is unpredictable as to whether the results obtained in human patients could be extrapolated to other organisms. Knowledge that when LAMC2 is over expressed a patient is less likely to respond to treatment with an EGFR inhibitor in one organism (i.e. humans) does not allow one to conclude that this phenomenon will also occur in other organisms. Additionally Knowledge that when GPC3 is over expressed a patient is more likely to respond to treatment with an EGFR inhibitor in one organism (i.e. humans) does not allow one to conclude that this phenomenon will also occur in other organisms. The specification does not teach phenomenon occurring in a representative number of different organisms. Additionally the mechanism of effect is unknown, thus the results obtained in humans can not be extrapolated to other organisms.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches patients who had elevated levels of LAMC2 were less likely to respond to a treatment with an EGFR inhibitor. The specification teaches patients who had elevated levels of GPC3 were more likely to respond to a treatment with an EGFR inhibitor. However the specification does not disclose which EGFR inhibitors were used to test this hypothesis. To identify the EFGR inhibitors that were

used for this study plus a representative number of the additional EFGR inhibitors would require extensive experimentation. For example, such experimentation may involve treating patients with a representative number of EFGR inhibitors and conducting multiple gene expression assays. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for predicating the likelihood that a colon cancer patient will respond to treatment with any EGFR inhibitor.

Working Examples:

The specification contains two working examples. The first working example deals with gene expression studies on head and neck tumors wherein the patients were treated with five different EGFR inhibitor drugs. However, the specification does not disclose which five EGFR inhibitors were used. The second working example deals with gene expression studies on colon caner wherein the patients were treated with an EGFR inhibitor. However, the specification does not disclose which EGFR inhibitor was used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the

art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach which EGFR inhibitors were used in the working examples. The specification does not teach a representative number of EGFR inhibitors. Further the specification does not teach a representative number gene products produced by LAMC2 and GPC3. Additionally, the disclosure of a single organism, humans, is not representative of the broadly claimed genus of all mammalian and non-mammalian subjects. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 35-39, 41-47, 51-52, 56-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 35-39, 41-47, 51-52, 59-61 are indefinite over the recitation of the following phrases in claim 1: "the normalized level", "the predictive transcripts", , and

"the corresponding gene product". There is insufficient antecedent basis for these limitations in the claims.

Claims 31, 35-39, 41-47, 51-52, 59-61 are indefinite over the recitation of the phrase "the transcript". The claim previously refers to predictive RNA transcripts but not to predictive transcripts in general, so it is unclear if these are the same or different.

Claims 31, 35-39, 41-47, 51-52, 59-61 are indefinite over the recitation of "corresponding gene product." Corresponding is not an art recognized term to describe the relationship between a RNA transcript and its gene product. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to an RNA transcript and its gene product, one of skill in the art cannot determine the meets and bounds of the claimed subject matter. Additionally it is unclear as to what is the product of an RNA transcript (i.e a protein, a splice variant, a mature RNA product).

Claims 41-47 are indefinite of the recitation of the phrase "the level of predictive RNA transcript or expression product thereof". This is unclear because the claim previously refered to a product of the RNA transcript but not to an expression product.

Claims 43 is indefinite over the recitation of the phrase "about 500 to about 5000". This phrase in considered unclear because "about 500 to about 5000" is not clearly defined in the specification and there is no art recognized definition for this phrase. For example, it is unclear as to whether "about 500 to about 5000" refers to 499 to 5001 or if it refers to 400-5100. Therefore the scope of the claim cannot be determined.

Claim 51 is indefinite over the recitation of the following phrases: "said fixed, paraffin embedded tissue", "the presence of a protease", "the lysis solution", "the wax solidifies", " the nucleic acid" and "said cooled lysis solution". There is insufficient antecedent basis for these limitations in the claims.

Claim 52 is indefinite of the recitation of the phrase "the use of a kit". The claim does not recite how the kit is to be used in the method of claim 31.

Claim 56 is indefinite over the recitation of the following phrases: "the expression level", "the gene product", and "said subject". There is insufficient antecedent basis for these limitations in the claims.

Claim 57 is indefinite over the recitation of the phrase "said subject". There is insufficient antecedent basis for this limitation in the claims.

Claim 59 is indefinite over the recitation of the following phrases: "said polynucleotides", and "said genes". There is insufficient antecedent basis for these limitations in the claims.

Claim 60 is indefinite over the recitation of the following phrases: "the prognostic transcript", "the increased normalized level", and "the corresponding gene product". There is insufficient antecedent basis for these limitations in the claims.

Claims 60 is indefinite over the recitation of the phrase "the transcript". The claim previously refers to predictive RNA transcripts but not to predictive transcripts in general, so it is unclear if these are the same or different.

Conclusion

5. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634
June 19, 2006

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER